Differential effects of dopamine agonists upon stimulated limbic and striatal dopamine release: *in vivo* voltammetric data

¹Jonathan A. Stamford, Zygmunt L. Kruk & Julian Millar

Department of Pharmacology (Physiology: JM), The London Hospital Medical College, Turner St, London E1 2AD

1 Fast cyclic voltammetry at carbon fibre microelectrodes was used in rats anaesthetized with chloral hydrate to monitor dopamine release in the caudate and nucleus accumbens evoked by electrical stimulation of the median forebrain bundle. Stimulation trains (50 Hz sinusoidal current, $100 \pm 10 \mu\text{A}$ r.m.s., 2 s duration) were repeated every 5 min throughout the experiment.

2 The actions of the dopamine agonists quinpirole, pergolide, SKF 38393, bromocriptine, (+)-3-(3-hydroxyphenyl)-N-n-propylpiperidine ((+)-3PPP) and (–)-3PPP were compared in the two nuclei.

3 Bromocriptine (10 mg kg^{-1} , i.p.) did not affect release in either nucleus while SKF 38393 caused a fleeting decrease in limbic but not striatal dopamine release at a high dose (20 mg kg^{-1} , i.p.).

4 Quinpirole and pergolide (both 1 mg kg^{-1} , i.p.) decreased stimulated dopamine release in the nucleus accumbens while in the caudate the drugs each caused a transient, though not quite significant, elevation of stimulated dopamine release followed by decrease in release of the same magnitude as that seen in the nucleus accumbens.

5 The (–)-enantiomer of 3PPP (20 mg kg^{-1} , i.p.), a partial agonist at the dopamine autoreceptor, increased stimulated dopamine release in both nuclei although the action in the caudate was larger and more prolonged. (+)-3PPP (20 mg kg^{-1} , i.p.), a full agonist, decreased release in the nucleus accumbens. A small, transient and not significant increase in the caudate was followed by decreased release.

6 The results are interpreted as being evidence for differences in the dopamine autoreceptor in the two nuclei, possibly in the affinity state of the receptor in each nucleus.

Introduction

Since its first demonstration *in vitro* (Farnebo & Hamberger, 1971) and *in vivo* (Kehr *et al.*, 1972) various groups have confirmed that dopamine agonists can decrease dopamine release or synthesis by an action at the nerve terminal level. These effects are receptor-mediated since they can be blocked by known dopamine antagonists. Since the receptors also respond to the endogenous transmitter they are termed 'autoreceptors' and are a potent means by which dopamine function is self-regulated. The nerve terminal autoreceptor is of the D_2 subtype (Stoof & Kebabian, 1984).

In recent experiments *in vivo* we were however surprised to observe that apomorphine, a commonly used agonist, appeared not to act as such in the caudate nucleus (CPu). Using voltammetry to measure the dopamine released by stimulation of the median forebrain bundle (MFB), we found that apomorphine reduced release in the nucleus accumbens (Acb) but was without any similar action in CPu. Indeed, the net effect was a slight, though not significant increase in release (Stamford *et al.*, 1987).

The purpose of the present study was to establish whether this effect of apomorphine was idiosyncratic or extended to other dopamine agonists. A series of dopamine agonists was therefore examined of differing D_1/D_2 selectivity, pre- and postsynaptic specificity and degree of partial to full agonist activity.

Methods

Animals

All experiments were performed on male Sprague-Dawley rats (250–350 g body weight) anaesthetized with chloral hydrate (400 mg kg^{-1} , i.p.). Anaesthesia was maintained throughout at

a depth sufficient to abolish corneal and hind limb withdrawal reflexes. Core temperature was monitored with a rectal probe and kept at $36.5 \pm 0.5^\circ\text{C}$ by means of a homeothermic blanket under the rat.

Rats were positioned in a stereotaxic frame according to the cranial orientation of Pellegrino *et al.* (1979). Small holes were made with a dental drill and rose-headed burr, over the Acb, CPu and MFB regions to allow implantation of the electrodes.

Carbon fibre microelectrodes (see below) were implanted, with a dual electrode carrier, into the Acb (AP: +3.3, L: +1.3, V: –6.5 mm: coordinates relative to bregma and the cortical surface) and CPu (AP: +1.8, L: +2.8, V: –4.5 mm). Histology revealed that electrodes implanted in Acb were located just medial to the anterior commissure and at the same dorsoventral level. Striatal electrodes were positioned centrally within the nucleus. The reference (Ag/AgCl) and auxiliary (stainless steel) were implanted at a convenient location in the neck muscle.

A small concentric bipolar stimulating electrode (Rhodes SNE 100) was located in the region of the MFB, as previously described (Ewing *et al.*, 1983). Initially, the electrode tip was inserted 6 mm below the cortical surface (AP: –2.2, L: +1.2 mm). Stimulation current was switched on and the electrode was lowered (1 mm min^{-1}) until dopamine release was detected at the carbon fibre working electrodes in the forebrain. Current was disconnected for a rest period of 10 min before starting the experiment.

Electrodes and electrochemistry

Glass-insulated carbon fibre microelectrodes ($8 \times 20 \mu\text{m}$ tip size) were prepared as previously described (Armstrong James & Millar, 1979). Electrodes were immersed in phosphate-buffered saline for 1 h before implantation *in vivo* to allow full equilibration of the surface. No electrochemical or chemical surface treatments of the electrodes were performed at any stage. Any electrode giving unstable charging current in buffer was discarded.

All electrochemical measurements were made by fast cyclic voltammetry (Millar *et al.*, 1985). The input voltage profile to

¹ Author for correspondence at present address: Department of Pharmacology, Faculty of Basic Medical Sciences, Queen Mary and Westfield College, Mile End Road, London E1 4NS.

the potentiostat consisted of 1.5 cycles of a 75 Hz triangular waveform (-1.0 to $+1.0$ V vs Ag/AgCl, 300 V s^{-1} scan rate) sweeping initially in the cathodic direction. With these scan parameters, dopamine oxidized at a peak potential of $+600$ mV vs Ag/AgCl. Pharmacological, anatomical and electrophysiological studies have shown that, following electrical stimulation of the MFB, dopamine is the sole compound detectable in the striatal and limbic forebrain at this potential (Millar *et al.*, 1985; Stamford *et al.*, 1988c). Current at $+600$ mV was monitored with sample-and-hold circuits for each working electrode. The outputs from the circuits were displayed on separate chart recorders and an oscilloscope. Voltammetric scans were applied alternately to the two carbon fibre working electrodes at a rate of 20 scans per electrode per second. At the end of each experiment the electrodes were calibrated in solutions of dopamine in phosphate-buffered saline.

Electrical stimulations

Electrical stimulations (50 Hz sinusoidal current, $100 \pm 10 \mu\text{A}$ r.m.s., 2 s train duration) were applied to the MFB at intervals of 5 min throughout the experiment. The first 6 stimulations acted as a control period. Peak dopamine release on these trains was averaged and expressed as 100%. Drugs or vehicle were administered immediately after stimulation 6 and their effects monitored for between 1 and 3 h.

Data presentation and statistics

Drug-induced changes in stimulated dopamine release were expressed as percentage changes (positive or negative) relative to the vehicle-treated controls. In each case, the changes in dopamine release in the controls were subtracted from those in the test animals to give the net effect (Stamford *et al.*, 1988a). Statistical comparisons of drug- and vehicle-treated animals were made by Mann Whitney U test. Peak dopamine release in CPu and Acb were compared by a paired *t* test.

Chemicals

Na_2HPO_4 , KH_2PO_4 and NaCl were obtained from BDH chemicals. Phosphate-buffered saline consisted of 0.15 M solutions of each phosphate salt in 0.85% w/v aqueous NaCl. The solutions were mixed in an approximately 4:1 ratio (Na:K salt) and then adjusted to pH 7.4 with smaller additions as necessary. Dopamine hydrochloride, tartaric acid and chloral hydrate were obtained from Sigma.

Drugs and dosing

The following drugs were used at the doses stated: Quinpirole (LY 171555) hydrochloride (1 mg kg^{-1}); bromocriptine mesylate (10 mg kg^{-1}); 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine (SKF 38393) hydrochloride (20 mg kg^{-1}); pergolide mesylate (1 mg kg^{-1}); (+) and (−)-enantiomers of 3-(3-hydroxyphenyl)-N-n-propylpiperidine (3PPP, 20 mg kg^{-1} each). The drugs were dissolved in 1% w/v tartaric acid and administered intraperitoneally in a dose volume of 0.33 ml per 100 g body weight. All drug doses refer to the base. Control animals received vehicle alone.

Results

Electrical stimulation of the MFB evoked dopamine release in both CPu and Acb. With the parameters used in the present study (50 Hz, $100 \pm 10 \mu\text{A}$, 2 s train), the stimulation gave a peak dopamine release in CPu of $3.11 \pm 0.31 \mu\text{M}$ (mean $\pm$ s.e.mean, $n = 43$). This was significantly ($P < 0.05$, paired *t* test) greater than in Acb ($2.48 \pm 0.21 \mu\text{M}$). Dopamine release could be evoked repetitively with stimulations applied every 5 min for 4 h or more. Dopamine release on successive stimu-

lations were reproducible and allowed drug effects to be quantified.

Figure 1 shows the effect of pergolide (1 mg kg^{-1} , i.p.) upon stimulated dopamine release over a 3 h period. Pergolide decreased limbic dopamine release (filled circles) by 30–40% over the course of the experiment. In CPu however (squares), the initial response was very variable although the group trend was a sharp elevation of release ($+50\%$) reaching significance ($P < 0.05$) at its maximum (20 min post-dosing). This response subsequently diminished and was superseded by a consistent inhibitory effect on dopamine release from about 80 min onward. The inhibition of dopamine release was of similar magnitude (50%) to that seen in Acb.

Bromocriptine (10 mg kg^{-1} , i.p.) had no effect on dopamine release over the 3 h test period (Figure 2). Stimulated dopamine release in both nuclei showed a high degree of variability with increasing time post dosing.

Figure 1 The effect of pergolide (1 mg kg^{-1} , i.p.) upon stimulated dopamine (DA) release in the caudate nucleus (■) and nucleus accumbens (●), expressed as a percentage change relative to the vehicle-treated controls (means are shown with s.e.mean indicated by vertical lines, $n = 7$). * $P < 0.05$; ** $P < 0.01$ vs vehicle controls (Mann Whitney U test).

Figure 2 The effect of bromocriptine (10 mg kg^{-1} , i.p.) upon stimulated dopamine (DA) release in the caudate nucleus (■), and nucleus accumbens (●) expressed as a percentage change relative to the vehicle-treated controls (means with s.e.mean shown by vertical lines, $n = 5$).

Figure 3 The effect of quinpirole (1 mg kg^{-1} , i.p.) upon stimulated dopamine (DA) release in the caudate nucleus (■) and nucleus accumbens (●) expressed as the percentage change relative to the vehicle-treated controls (means with s.e.mean shown by vertical lines, $n = 6$). * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs vehicle controls (Mann Whitney U test).

The action of quinpirole (1 mg kg^{-1} , i.p.) was similar to that of pergolide (Figure 3). In Acb, quinpirole caused a rapid (onset 15 min) and sustained decrease (50%) in stimulated dopamine release. However, in CPu there was generally an initial sharp rise (+30%) in dopamine release although a few animals showed a decrease. This heterogeneity was reflected in the group data such that the increase narrowly failed to reach significance. As with pergolide, this effect was followed by inhibition of dopamine release from about 100 min onwards.

SKF 38393 (20 mg kg^{-1} , i.p.) caused a fleeting reduction in stimulated limbic dopamine release (Figure 4). The effect was only observed for 20 min and was not matched by any action on dopamine release in CPu.

The effects of the enantiomers of 3PPP were studied over a period of 1 h. 3PPP is electroactive and could thus be detected *in vivo* with a broad oxidation current peaking at greater than +1000 mV vs Ag/AgCl. Nevertheless simultaneous detection of 3PPP did not affect the ability to detect changes in stimulated dopamine release above this elevated background signal. Following intraperitoneal administration, peak brain levels of

Figure 4 The effect of SKF 38393 (20 mg kg^{-1} , i.p.) upon stimulated dopamine (DA) release in the caudate nucleus (■) and nucleus accumbens (●) expressed as the percentage change relative to the vehicle-treated controls (means with s.e.mean shown by vertical lines, $n = 6$). * $P < 0.05$; ** $P < 0.01$ vs vehicle controls (Mann Whitney U test).

Figure 5 Effects of (-)-3PPP (a) and (+)-3PPP (b), both at 20 mg kg^{-1} , i.p., upon stimulated dopamine (DA) release in the caudate nucleus (■) and nucleus accumbens (●) expressed as the percentage change relative to the vehicle-treated controls (means with s.e.mean shown by vertical lines, $n = 5$). * $P < 0.05$; ** $P < 0.01$ vs vehicle controls (Mann Whitney U test).

3PPP occurred after about 20–30 min. The enantiomers of 3PPP had very different effects on dopamine release (Figure 5). (-)-3PPP elevated dopamine release (Figure 5a) in both CPu and Acb although the action in CPu was larger and of longer duration. (+)-3PPP decreased dopamine release in ACb (Figure 5b) while the action in CPu was qualitatively similar to pergolide and quinpirole: a small elevation (not significant) followed by a decrease in release.

Discussion

The experimental procedure used in the present study functionally isolates the nerve terminal from the cell body. Actions of drugs at the cell body autoreceptor alter the firing rate of the neurones. However, the present methodology prevents drug effects in the substantia nigra or ventral tegmental area from influencing those in the terminals since the protocol measures stimulated, not basal, dopamine release. Since the stimulating electrode is positioned in the MFB, impulse traffic to the terminals is controlled at this point rather than in the cell bodies. Drugs such as SCH 23390 that have no effect on the nerve terminal autoreceptor, but which increase cell firing (Mereu *et al.*, 1985) and hence dopamine metabolism (Saller & Salama, 1986) have no observable action on stimulated dopamine release in the present protocol (Stamford *et al.*, 1988a). Thus the methodology, in effect, measures the actions of drugs at the level of the nerve terminal. Although we cannot firmly

exclude actions upon local microcircuitry, preliminary experiments in our laboratory have failed, for example, to show any effect of cholinergic agonists or antagonists upon stimulated striatal dopamine release (Stamford unpublished) although this action is readily demonstrable *in vitro* (Lehmann & Langer, 1982) and might be expected to exert some local non-autoreceptor mediated control of dopamine release *in vivo*. Thus we cautiously propose that the present protocol measures solely effects at terminal dopamine autoreceptors.

The purpose of the study was to establish whether the previously seen effect of apomorphine (Stamford *et al.*, 1987) was observable with other agonists and which properties of the agonist might be responsible. Apomorphine is equipotent at D_1 and D_2 receptors (Andersen *et al.*, 1987; Seeman *et al.*, 1986). Thus, drugs were chosen which ranged from the selective D_1 agonist SKF 38393 (Setler *et al.*, 1978) to the D_2 agonist quinpirole (Stoof & Kebabian, 1984). Apomorphine also does not discriminate between pre- and postsynaptic dopamine receptors (Helmreich *et al.*, 1982) and thus drugs with mainly postsynaptic or presynaptic actions were used (bromocriptine and 3PPP respectively – Seeman, 1981; Watling, 1982). The doses chosen for each drug were selected to be in the middle to upper half of the dose-range described in the literature.

SKF 38393, the D_1 agonist (Setler *et al.*, 1978), had no effect on stimulated dopamine release in CPu over the 3 h post administration (Figure 4). In Acb the drug caused a transient decrease in dopamine release. The brevity of this effect and the absence of parallel action in CPu make it likely that the result is artefactual. SKF 38393 exerts D_1 receptor-mediated effects at $1.25\text{--}4.0\text{ mg kg}^{-1}$ (Andersen *et al.*, 1987; Braun & Chase, 1986) and has a D_1 type cooperative action on postsynaptic D_2 receptor-related behaviours at doses as low as 0.25 mg kg^{-1} (Sonsalla *et al.*, 1988). It is likely that the effect seen in the present study is a reflection of the high dose used. For instance, Imperato & Di Chiara (1988) showed that SKF 38393 applied locally at high concentration could decrease dopamine release in CPu in a manner unrelated to D_1 or D_2 receptor activation.

Bromocriptine (10 mg kg^{-1} , i.p.) had no effect on dopamine release in either nucleus (Figure 2). This is consistent with the reported postsynaptic selectivity of this drug (Jenner *et al.*, 1979). Bromocriptine has been shown to induce clear circling behaviour in rats at doses much lower than used here (Costall *et al.*, 1975). Bromocriptine is also found to be substantially less potent than apomorphine in several models of dopamine autoreceptor activity (Westfall *et al.*, 1983; Yarbrough *et al.*, 1984).

Pergolide (1 mg kg^{-1} , i.p.) and quinpirole (1 mg kg^{-1} , i.p.) evoked similar responses (Figures 1 and 3 respectively). In both cases the drugs caused a substantial reduction of stimulated dopamine release in Acb with a rapid onset of action (10–15 min). In CPu the drugs usually caused an initial elevation of stimulated dopamine release (with pergolide, significantly so). This was followed, after about an hour, by a reduction in release of similar magnitude to that in Acb. In both cases the actions of the drugs in each nucleus were qualitatively the same as those obtained for apomorphine (Stamford *et al.*, 1987).

Both pergolide and quinpirole have higher potency at D_2 than D_1 receptors (Andersen *et al.*, 1985). This and the absence of effect with SKF 38393 mean that the unusual caudate response of apomorphine is likely to be the result of D_2 receptor activity. This is supported by the fact that it is blocked by haloperidol (Stamford *et al.*, 1987). The lack of effect of bromocriptine also indicates that the response is mediated by presynaptic D_2 receptors.

Although the data suggest that the unusual effect seen in CPu is due to presynaptic D_2 receptor activation, the same conclusion applies to Acb where a classical agonist response was observed. The question of why the CPu response differs so markedly from the expected effect remains unanswered. This was therefore further investigated with the 3PPP enan-

tiomers. (+)-3PPP is an agonist at both pre- and postsynaptic D_2 receptors (Clark *et al.*, 1985) while (–)-3PPP is a partial agonist at the autoreceptor whose effect is determined by the ongoing level of endogenous transmitter activity (Hjorth *et al.*, 1987). In the present study (+)-3PPP behaved as an autoreceptor agonist in CPu although the effect was slower in onset and less pronounced than in Acb (Figure 5). (–)-3PPP however showed strong autoreceptor 'antagonist' behaviour in CPu as previously reported (Arbilla & Langer, 1984). A very small potentiation of dopamine release was transiently observed in Acb.

The partial agonist action of (–)-3PPP provides a clue to possible interpretation of the data. The action of an autoreceptor agonist is determined, in part, by the existing 'tone' at the receptor (see Kenakin, 1987). In a circumstance where there is little endogenous transmitter activity, the effect of an agonist will be at least additive and thus inhibit transmitter release. It is reported, for example, that the autoreceptor activity of the dopamine agonists is most pronounced at low stimulation frequencies (Hoffmann *et al.*, 1986). However, at receptors that are maximally activated already, any agonist with less than full intrinsic activity will compete with the transmitter and behave functionally as an antagonist, as seen here with (–)-3PPP.

A qualitatively similar effect would be expected with different affinity states of the same receptor. A high affinity receptor would be maximally stimulated at a low transmitter level and thus agonists would compete with the transmitter and behave essentially as antagonists. Conversely, a low affinity receptor might not be fully activated and thus have room for further agonist stimulation.

The dopamine D_2 receptor can exist in two states: the high affinity state has a dissociation constant (K_d) for dopamine of 5 nM while the low affinity state has a K_d of 4 μM (Seeman *et al.*, 1986). These two levels are interconvertible and the state of the receptor expressed can be modified by, amongst others, guanine nucleotides (Mackenzie & Zigmond, 1984), temperature (Watanabe *et al.*, 1985), sodium and calcium ions (Hamblin *et al.*, 1984; Urwyler, 1987).

An explanation for the data of the present study (and previous report on apomorphine; Stamford *et al.*, 1987) can be made by postulating different autoreceptor states in CPu and Acb. In Acb, for instance, the agonists' action would be consistent with the autoreceptor existing in a low affinity state ($K_d = 4\text{ }\mu\text{M}$). Thus peak dopamine release on stimulation ($2.48\text{ }\mu\text{M}$) would not cause maximal activation and agonists would be able to stimulate the receptor and thus inhibit release. Conversely, agonist action in CPu can be explained by a high affinity state. At this K_d (5 nM) the receptor would be saturated by the dopamine levels attained on stimulation ($3.11\text{ }\mu\text{M}$). Agonists with lower intrinsic activity would thus compete with the dopamine, and, to some extent, antagonize its effect.

Support for this hypothesis is obtained from the later effects of pergolide and quinpirole, where the CPu response shifts from functional 'antagonism' to the same effect as in Acb. It is established that prolonged activation can desensitize the autoreceptor (Arbilla *et al.*, 1985). One might thus expect persistent agonist exposure to cause high affinity sites to convert to the lower affinity state of the autoreceptor. Such interconversion has been shown to occur over a period of 15–30 min (Levesque & Di Paolo, 1988) and thus could explain the shift in response to pergolide and quinpirole seen over a similar time frame. No change occurred in Acb since the receptors were already (according to the hypothesis) in the low affinity state.

The hypothesis is further supported by two related studies from our laboratory. In the first we compared the diffusion and uptake of dopamine in CPu and Acb and observed a lower density of dopamine uptake sites in Acb (Stamford *et al.*, 1988b). The fewer uptake sites allow dopamine to exist longer in the extracellular space and thus may mean that autoreceptors are more persistently stimulated in Acb. This, in

turn, would be expected to lead to desensitization. In CPu, which has more uptake sites, the autoreceptors may be less exposed to dopamine and consequently exist in the high affinity state, as previously postulated (Seeman & Grigoriadis, 1987). The fact that stimulated dopamine release in the CPu is greater than in Acb may reflect other differences in the dopamine innervation of the two nuclei such as the relative size of the releasable and storage dopamine pools or a higher release rate in response to externally imposed impulse traffic.

In a second related set of experiments we compared the regional effects of dopamine antagonists (Stamford *et al.*, 1988a). Overall, the antagonists showed a greater potentiation of dopamine release in CPu than Acb, as would be predicted by the hypothesis of a different autoreceptor affinity state in the two nuclei. The proposed high affinity striatal receptor, being maximally activated by ongoing dopamine release, would be expected to show a greater response to subsequent

blockade than the partially activated low affinity limbic autoreceptor.

In conclusion, although one cannot exclude the possibility that the drugs interact with other receptors or that differences in local circuitry underlie the drug effects, it is possible to say that the previously reported unusual CPu response to apomorphine is matched only by those drugs that are agonists at presynaptic D₂ receptors. Taking the various strands of evidence together, we interpret the results of the present study as indicating that dopamine agonists exert actions on stimulated striatal and limbic dopamine release that are the result of their own intrinsic activity at D₂ receptors and the affinity state of the autoreceptor.

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